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## Framing atopic dermatitis topical medication application site discomfort as a signal of efficacy improves willingness to continue use

*To the Editor:* Medications for atopic dermatitis (AD) can cause application site discomfort, leading patients to discontinue therapy. We assessed whether framing application discomfort as a sign of efficacy affects patients' willingness to tolerate application site discomfort.

After institutional review board approval, adults with self-reported AD were randomized to 1 of 9 hypothetical scenarios about their physician prescribing a cream for AD (Table I) administered by online survey (Amazon Mechanical Turk).[1] Each of the 9 scenarios was composed of a combination of 3 sensations—painful sensation; no painful sensation; and neutral, nonpainful sensation—and 3 sensation framings—control, counseling of potential sensation, and sensation is a sign the medication is working. Willingness to continue use of the medication was assessed using a 9-point Likert-type scale. The results were analyzed using R, version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria) with a 2-tailed, independent-sample $t$ test, analysis of variance (ANOVA), $\chi^2$, and Cohen's $d$.

The 1039 participants represented both sexes and a wide range of ages, races, ethnicities, and education levels, with no statistically significant differences in demographics between groups (Supplemental Table I available via Mendeley at https://doi.org/10.17632/n96f27nypz.1#file-563538aa-0cf5-4244-8cc2-d7ac908e7ec9). Participants randomly assigned to a hypothetical scenario where they experienced a burning or stinging sensation reported being less willing to continue medication use than participants who did not experience a sensation or experienced a neutral, nonpainful sensation (both $P < .001$; Table II). For an unpleasant sensation with topical medication use, counseling to expect a sensation improved participants' willingness to continue use of a medication ($P < .001$; $d = .46$). However, when participants were counseled that the sensation is a signal of efficacy, their reported willingness greatly increased ($P < .001$; $d = 1.32$). Framing the discomfort as a signal of efficacy negates the effect of the discomfort compared with no painful sensation ($P = .42$) and a neutral, nonpainful sensation ($P = .96$). Even if participants did not feel a painful sensation when forewarned that it is a signal of efficacy (which may be interpreted as the medication's lack of efficacy), this did not detrimentally affect their willingness to continue medication use ($P = .57$).

Although guidelines[2,3] recommend that physicians counsel patients to expect transient application site discomfort, how effective this counseling is or the most effective means of counseling is not well characterized. In our study, positive framing of adverse effects was not tested for improved efficacy of the medication (as it is survey based), but instead, reported willingness to continue treatment was assessed. Improving willingness and adherence are critical in AD because adherence to topical corticosteroids is abysmal, declining to 32% over just 8 weeks.[4] Topical calcineurin inhibitors and crisaborole have high rates of application site discomfort compared with topical corticosteroids and may be even more affected by poor adherence.[5] Many cognitive biases affect patient adherence

**Table I.** Survey script scenario variants*—All scenarios: Your physician prescribes a medicated cream for atopic dermatitis …

| Groups | 1: Painful sensation (burning and stinging sensation) | 2: No painful sensation (no burning and stinging sensation) | 3: Neutral, nonpainful sensation (cooling sensation) |
|---|---|---|---|
| A: Control | When you apply this medication to your skin for the first time, there is a burning and stinging sensation. | When you apply this medication to your skin for the first time, there is **no** burning or stinging sensation. | When you apply this medication to your skin for the first time, there is a cooling sensation. |
| B: Counseling of potential sensation | *He warns you that this medication may cause a stinging or burning sensation.* When you apply this medication to your skin for the first time, there is a burning and stinging sensation. | *He warns you that this medication may cause a stinging or burning sensation.* When you apply this medication to your skin for the first time, there is **no** burning or stinging sensation. | *He warns you that this medication may cause a cooling sensation.* When you apply this medication to your skin for the first time, there is a cooling sensation. |
| C: Sensation is a sign the medication is working | *He warns you that this medication may cause a stinging or burning sensation and that this **is a sign the medication is working.*** When you apply this medication to your skin for the first time, there is a burning and stinging sensation. | *He warns you that this medication may cause a stinging or burning sensation and that this **is a sign the medication is working.*** When you apply this medication to your skin for the first time, there is **no** burning or stinging sensation. | *He warns you that this medication may cause a cooling sensation and that this **is a sign the medication is working.*** When you apply this medication to your skin for the first time, there is a cooling sensation. |

*The participant questionnaire contained unformatted text. Assessment: *How willing are you to continue use of this medication?* on a 9-point Likert-type scale, with 1 as *strongly not willing* and 9 as *strongly willing*.

**Table II.** Overview of scenario variants and results

| Group (n) | Application site sensation | Counseling of potential sensation | Counseling that sensation is a signal of efficacy | Direction of efficacy signaling | Willingness, mean (SD) | *P* value; Cohen *d** (compared with control [1A, 2A, 3A]) |
|---|---|---|---|---|---|---|
| Painful sensation | | | | | | |
| 1A (118) | Discomfort | - | - | - | 4.4 (1.9) | - |
| 1B (116) | Discomfort | + | - | - | 5.3 (1.9) | <.001; .46 |
| 1C (118) | Discomfort | + | + | Working | 6.9 (1.8) | <.001; 1.32 |
| No painful sensation | | | | | | |
| 2A (118) | None | - | - | - | 7.1 (1.8) | - |
| 2B (113) | None | + | - | - | 7.0 (1.9) | .89 |
| 2C (113) | None | + | + | Not working | 6.9 (1.9) | .57 |
| Neutral, nonpainful sensation | | | | | | |
| 3A (112) | Neutral | - | - | - | 6.9 (1.7) | - |
| 3B (117) | Neutral | + | - | - | 7.0 (1.8) | .72 |
| 3C (114) | Neutral | + | + | Working | 7.6 (1.7) | .002; .41 |

*SD,* Standard deviation.
*Cohen's *d*: a small effect size is considered approximately 0.2, medium is approximately 0.5, and large is greater than 0.8.

(Supplemental Table II available via Mendeley at https://doi.org/10.17632/n96f27nypz.1#file-563538aa-0cf5-4244-8cc2-d7ac908e7ec9)—omission bias, the tendency to favor inaction even when that action is known to have benefit, and present bias, where the value of future improvement is underweighted relative to the short-term unpleasant sensation, may be factors mitigated by the framing studied here. Although counseling on what to expect is useful, targeted counseling to frame the sensation as a signal of efficacy may bring an even greater effect.

Limitations of this study are that the results are based on hypothetical statements assessed with reported willingness to continue medication use

and that participants enrolling in a survey may be more affected by framing than real-world populations.

Counseling to anticipate application site discomfort and framing such discomfort as a sign of efficacy may be a potential tool to enhance AD topical medication adherence.

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## Ambient ultraviolet radiation and major salivary gland cancer in the United States

*To the Editor:* Risk of major salivary gland cancer (SGC) increases after a diagnosis of skin cancers,[1,2] suggesting a shared risk factor such as exposure to ultraviolet radiation (UVR). However, the evidence supporting this association is limited.[3,4]

We examined the relationship between ambient UVR and risk of SGC by race/ethnicity and histologic subtype using data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry program linked to US county-level, satellite-based ambient UVR. SEER counties were ranked by UVR and assigned quartiles 1 to 4 (lowest to highest) (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/ccsywx9fgx.2). Incidence rate ratios and 95% confidence intervals were calculated by using mixed-effects Poisson regression, adjusting for sex, attained age, year, and race and including SEER registry as a random effect. Numbers of SGC cases by sex and more than 20 subtypes in 2000 through 2016 are shown in Supplemental Table I (available via Mendeley at https://doi.org/10.17632/ccsywx9fgx.2). Incidence of squamous cell carcinoma subtype (SCCSGC) in non-Hispanic white individuals was significantly higher than in those of other races/ethnicities (Supplemental Table II; available via Mendeley at https://doi.org/10.17632/ccsywx9fgx.2).

UVR was significantly associated with increased risks of SCCSGC in non-Hispanic white individuals ( per 10 $mW/m^2$; UVR incidence rate ratios, 1.18; 95% confidence interval, 1.08-1.28; $P = .0002$). However, no association was found for other subtypes and in other races/ethnicities (Fig 1).